Parkinsonism

Presented by:

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Objectives:

What is parkinson disease
Pathophysiology and causes
Lines of therapy
Parkinsonism:

Definition:

Parkinsonism is a progressive neurological disorder of muscle movement as a clinical syndrome consisting of 4 cardinal features:

1) bradykinesia (slowness of movement) and, in extreme cases, a loss of physical movement (akinesia)

2) muscular rigidity

3) resting tremor (which usually disappears during voluntary movement)

4) impairment of postural balance leading to disturbances of gait and falling
PARKINSON’S DISEASE

- Onset usually gradual, after age 50.
  (Slowly progressive)

- Mask-Like, Blank Expression

- Stooped Posture

- Pill Rolling Tremors

Tremor
- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

Bradykinesia
- Loss of normal arm swing while walking
- ↓ Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement

- Possible Mental Deterioration

Depression

Muscle Rigidity
- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs in Black Population

Shuffling, Propulsive Gait
Parkinson's Disease
Causes of parkinsonism:

1) **Idiopathic PD:**
   - Due to loss of dopaminergic neurons of the substantia nigra
   - Progressive loss of dopamine-containing neurons is a feature of normal aging; however, most people do not lose the 70% to 80% of dopaminergic neurons required to cause symptomatic PD
   - Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism

2) **Secondary PD:**
   - e.g., following stroke, drugs (antipsychotic, antiemetic), viral encephalitis, toxicity by heavy metal and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), head injury, drugs as metocloperamide, haloperidol, chlorpromazine.
Decreased amount of dopamine

Normal amount of acetylcholine
Treatment of parkinsonism

• Aim of treatment is to enhance dopaminergic pathway or inhibit cholinergic pathway in the brain
Agents that Increase Dopamine functions

- Increasing the synthesis of dopamine - **l-Dopa**
- Inhibiting the catabolism of dopamine – **selegiline, entacapone**
- Stimulating the release of dopamine - **amphetamine**
- Stimulating the dopamine receptor sites directly - **bromocriptine & pramipexole**
- Blocking the uptake and enhancing the release of dopamine – **amantadine**

**Drugs acting on cholinergic system**

- Central anticholinergics – *Teihexyphenidyl (Benzhexol), Procyclidine, Biperiden*
- Antihistaminics – *Orphenadrine, Promethazine*
• Dopamine itself does not cross the blood-brain barrier and therefore has no CNS effects. However, levodopa, as an amino acid, is transported into the brain by amino acid transport systems, where it is converted to dopamine by the enzyme L-aromatic amino acid decarboxylase.
Drugs used in the treatment of parkinsonism

1- Levodopa (1)

Levodopa is *(the most effective)* drug used in the treatment of parkinsonism.

**Chemistry:**
- It is the metabolic precursor of dopamine.

**Mechanism of action:**
- In the brain, levodopa is converted to dopamine by decarboxylation. The dopamine produced is responsible for the therapeutic effectiveness of the drug in PD; after release, it is either transported back into dopaminergic terminals by the presynaptic uptake mechanism or metabolized by the actions of MAO and catechol-\(O\)-methyltransferase (COMT).
Drugs used in the treatment of parkinsonism

1- Levodopa (2)

– If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the peripheral sites so that little unchanged drug reaches the cerebral circulation. (98% is decarboxylated to dopamine in gut and liver)

– 1 - 2% crosses BBB, taken up by neurones and DA is formed

• In addition, dopamine release into the circulation by peripheral conversion of levodopa produces undesirable effects,
Drugs used in the treatment of parkinsonism

1- Levodopa (3)

- In practice, levodopa is administered in combination with a peripherally acting inhibitor of decarboxylase, such as carbidopa, Benserazide that do not penetrate into the CNS.

- Inhibition of peripheral decarboxylase markedly increases the fraction of administered levodopa that crosses the blood-brain barrier and reduces the incidence of peripheral side effects.

- The most commonly prescribed form of carbidopa/levodopa is the 25/100 form, containing 25 mg carbidopa and 100 mg levodopa.
CLINICAL USE:

• Early use lowers mortality rate
• Combined with Carbidopa
• Sinemet – dopa preparation containing levodopa in fixed proportion (1:10 or 1:4)
  Sinemet 25/100 TID
• 30 -60 minutes before meals
  – Bradykinesia and Rigidity Respond Quickly
  – Reduction in Tremor Effect with Continued therapy
  – Handwritting, speech, facial expression and interest in life improves gradually
  – L Dopa less Effective in Eliminating Postural Instability and Shuffling Gait
Does not stop the progression of Parkinsonism • Early therapy lowers mortality rate. • Best results initially for 1-3 yrs. • Benefit decrease in 3-4 yrs because it is a degenerative disease & number of dopaminergic neurons gradually decreases, insufficient to take up Levodopa for conversion into Dopamine.
Benefits of adding peripheral decarboxylase inhibitor:

Plasma $t_{1/2}$ – prolonged
Dose of levodopa – 30% reduction
Reduction in systemic complications
((Nausea and Vomiting – less
Cardiac – minimum complications))
Pyridoxine reversal of levodopa – do not occur
On/Off effect – minimum
Better overall improvement of patient
Drugs used in the treatment of parkinsonism

1- Levodopa (4)

Adverse effects:
A) Central:

1) long-term therapy leads to "wearing off" phenomenon: each dose of levodopa improves mobility for 1 to 2 hours, but rigidity and akinesia return at the end of the dosing interval. Increasing the dose and frequency of administration can improve this situation, but this often is limited by the development of dyskinesias (excessive and abnormal involuntary movements). Patients may fluctuate between being "off," having no beneficial effects from their medications, and being "on" but with dyskinesias, a situation called the on/off phenomenon.
To reduce the possibilities of *on/off phenomenon*.

Controlled release prep. of Sinemet.

Decrease dietary protein to minimum ----taken in evening.

Addition of Dopaminergic agonists (Pramipexole, Ropinirole, Pergolide, Bromocriptine).

Addition of selegiline
Drugs used in the treatment of parkinsonism

1- Levodopa (5)

2) Mental effects
   Depression, anxiety, agitation, insomnia, delusions, hallucinations, euphoria

3) Dyskinesias (excessive and abnormal involuntary movements) as chorea and tremor
   • Behavioural effects:
     – 20 to 25% of Population
     – Trouble in Thinking (Cognitive Effects)
     – Hypomania - Inappropriate Sexual Behavior; "Dirty Old Man"
   • Stop All Medication for 3-21 Days and Then Slowly Reinitiate Therapy to Gradually increasing doses. - *Drug Holiday*
Drugs used in the treatment of parkinsonism

1- Levodopa (6)

B. Peripheral:

Due to formation of dopamine peripherally

1. The most common peripheral side effects are anorexia, nausea, and vomiting (likely due to dopamine’s stimulation of the CTZ in the medulla oblongata). (80% of patients)

2. Cardiovascular side effects in the form of orthostatic hypotension (30% of patients) and cardiac arrhythmias, angina, tachycardia

☐ Abrupt withdrawal of levodopa may precipitate the neuroleptic malignant syndrome.
Other adverse effects

- mydriasis, blood dyscrasias, hot flushes, gout, brownish discoloration of the urine & saliva, abnormal smell, priapism, transient elevations of transaminases
Drugs used in the treatment of parkinsonism

1- Levodopa (7)

**Drug Interactions:**

1. Pharmacologic doses of **pyridoxine** (vitamin B6) enhance the extracerebral metabolism of levodopa and prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken.

2. Levodopa should not be given to patients taking **monoamine oxidase A inhibitors** or within 2 weeks of their discontinuance, because such a combination can lead to hypertensive crises.

3. **Anticholinergics** – synergistic action but delayed gastric emptying – reduced effect of levodopa
Drugs used in the treatment of parkinsonism

1- Levodopa (7)

Contraindications

1. Psychotic patients
2. Angle-closure glaucoma
3. Cardiac disease
4. Peptic ulcer
5. Melanoma
Drugs used in the treatment of parkinsonism

2- Dopamine receptor agonists (1)

• Four orally administered dopamine-receptor agonists are available for treatment of PD:
  1) Ergot derivatives: as bromocriptine or pergolide
  2) Non ergot derivatives as PRAMIPEXOLE, Ropinirole, Rotigotine (Used in early PD as Transdermal patch)
Dopamine receptors agonists

- Almost similar therapeutic action
- Relieves clinical symptoms of PD
- Duration of action is longer than L-dopa (8-16 Hrs)
- Effective in patients with on/off phenomenon
- Side effects like confusions, hallucinations similar to l-dopa
- 1st dose effect – orthostatic hypotension
ERGOT ALKALOIDS:

• BROMOCRIPTINE (Parlodel)
  – D2 agonists
  – Endocrinologic disorders (hyperprolactinemia)
  – Absorbed variably in GIT
  – Peak plasma levels: 1-2 hrs
  – 7.5 mg & 30 mg
  – 1.25 mg BID after meals X 2-3 months and increase 2.5 mg q 2 wks
ERGOT ALKALOID:

- PERGOLIDE
  - Stimulates both D1 and D2
  - 3 mg daily
  - 0.05 mg starter dose
  - More effective than bromocriptine
NON-ERGOT DOPAMINE AGONISTS:

- **PRAMIPEXOLE**
  - Preferential affinity to D3
  - Monotherapy is effective in mild cases & with L-dopa in advanced with fluctuation in response
  - Rapidly absorbed
  - Peak plasma concentration: 2 hrs
  - 0.125 mg TID then doubled after 1 wk
  - Increments of 0.75 mg at weekly intervals
NON-ERGOT ALKALOIDS:

• ROPINIROLE
  – Pure D2 receptor agonists
  – 0.25 mg TID then total daily dose is increased by 0.75 mg at weekly intervals until the 4th wk & increased by 1.5 mg thereafter
ADVERSE EFFECTS:

- GIT: anorexia, nausea, vomiting, bleeding PUD, reflux esophagitis
- Cardiovascular: postural hypotension, painless digital vasospasm
- Dyskinesias
- Mental disturbances
CONTRAINDICATIONS:

- History of psychotic illness
- Recent myocardial infarction
- Peripheral vascular disease
- Peptic ulceration
Drugs used in the treatment of parkinsonism

3- Monoamine oxidase inhibitors (1)

Two types of monoamine oxidase (MAO) have been distinguished. Monoamine oxidase (A) metabolizes norepinephrine and serotonin; monoamine oxidase (B) metabolizes dopamine.

Selegiline:

Mechanism of action:
• Selective inhibitor of monoamine oxidase B (retards the breakdown of dopamine). Given alone, it has a weak action. It is therefore used as adjunctive therapy for patients with a declining response to levodopa.

Side effects:
• May cause insomnia when taken later during the day.

Drug interactions:
• It should not be taken by patients receiving tricyclic antidepressants, or serotonin reuptake inhibitors because of the risk of acute toxic interactions.
• The adverse effects of levodopa may be increased by selegiline.
SELEGELINE

• 5 mg with breakfast & lunch
• Cause insomnia when taken later during the day
• Not to be taken with meperidine, TCAs, SSRIs
• Increase adverse effects of levodopa
• Selegiline can be used in mild early PD
• Add -on to levodopa in early cases
  – Prolong levodopa action
  – Reduction in dose of levodopa
  – Reduces motor fluctuations
  – Decreases wearing off phenomenon
  – Advance cases of on/off – not improved
  – Levodopa side effects (hallucinations) etc, worsens
  – Rasagiline: 5 times more potent than selegiline
Drugs used in the treatment of parkinsonism

3- Catechol O methyl transferase inhibitors (1)

Tolcapone

• **Mechanism of action:**

1. **Inhibit** catechol O methyl transferase (COMT) which is responsible for the conversion of dopa into methyl dopa.
2. **prolong the action of** levodopa by diminishing its peripheral metabolism.

• These agents may be helpful in patients receiving levodopa to reduce dose and decrease fluctuations in response
• Side effects are similar to levodopa
CATHECOL-O-METHYLTRANSFERASE INHIBITORS:

- **TOLCAPONE** - central & peripheral metabolism
- **ENTACAPONE** *(SELECTIVE)*
  - peripheral metabolism
  - Prolongs the duration of levodopa by decreasing its peripheral metabolism
  - Helpful in patients receiving levodopa who have fluctuations
  - $t_{1/2} = 2\text{ hrs}$
  - Both are available in fixed dose combinations with levodopa/carbidopa
STALEVO

• Combination of levodopa with both carbidopa and entacapone
• Simplifies drug regimen
• Requires consumption of a lesser number of tablets
Drugs used in the treatment of parkinsonism

4- Amantadine(1)

Amantadine, an antiviral agent. Its mode of action in parkinsonism is unclear

Clinical Use

- Amantadine is less potent than levodopa and its effects disappear after only a few weeks of treatment peak plasma concentration: 1-4 hrs after oral dose 100 mg BID-TID
- Plasma t½ = 2-4 hrs

Adverse Effects

1. Central nervous system effects, seizure
2. Peripheral edema
3. Headache
4. Heart failure
5. Postural hypotension
6. Urinary retention
7. Gastrointestinal disturbances (eg, anorexia, nausea, constipation, and dry mouth).

Contraindications

- Amantadine should be used with caution in patients with a history of seizures or heart failure.
ACETYLCHOLINE BLOCKING AGENTS:

• Improve tremor & rigidity of parkinsonism but have little effect in bradykinesia
  • Benztropine mesylate
  • Biperiden
  • Orphenadrine
  • Procyclidine
  • Trihexyphenidyl
Drugs used in the treatment of parkinsonism

5- Acetylcholine blocking drugs(1)

- Benztropine

Clinical Use

- Antimuscarinic drugs may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.
Adverse Effects

1) Central nervous system effects, including drowsiness, restlessness, confusion, agitation, hallucinations, and mood changes. Dyskinesias occur in rare cases.

2) Atropine – like actions: dryness of the mouth, blurring of vision, urinary retention, nausea and vomiting, constipation, tachycardia, palpitations, and cardiac arrhythmias. Withdrawal should be gradual in order to prevent acute exacerbation of parkinsonism.

Contraindications

1. Prostatic hyperplasia,
2. Obstructive gastrointestinal disease (eg, paralytic ileus)
3. Angle-closure glaucoma.
- **Neural tissue transplants**--Researchers are studying ways to implant neural tissues from fetal pigs into the brain to restore the degenerate area. In a clinical trial conducted in part at Boston University School of Medicine, three patients out of 12 implanted with the pig tissues showed significant reduction in symptoms.

- **Genetic engineering**--Scientists are modifying the genetic code of individual cells to create dopamine-producing cells from other cells, such as those from the skin.

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